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PANTOTHENIC ACID:
ITS HISTORY AND CHEMISTRY

BORDEN'S REVIEW
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PANTOTHENIC ACID
ITS HISTORY AND CHEMISTRY

Although pantothenic acid is usually classified as one of the newer members of the vitamin B complex, it has one of the oldest histories among the vitamins with respect to recognition of its biological activity. Its discovery, early in the 1930's, and its subsequent synthesis about ten years later mark not the beginning, but the peak of a long and exciting hunt for a mysterious substance whose very existence had been clouded in doubt and uncertainty for many years.

The mystery is now clarified and pantothenic acid has emerged as a specific vitamin factor. Numerous investigations indicate it to be an essential factor for all living matter, both plant and animal. A wide variety of characteristic deficiency symptoms, including disturbances of the skin and hair, degeneration of various internal organs, and lesions of the nervous system, have been attributed directly to a lack of pantothenic acid. These disorders have been studied extensively in many animals, including rats, mice, chickens, hogs, foxes and dogs. Aside from findings of experimental significance in these cases, knowledge of the essential role of pantothenic acid in the physiological processes of animals has contributed much to practical and economic problems in animal husbandry.

The investigation of pantothenic acid in its role as a nutritional essential for man has begun only recently. Nevertheless, on the basis of animal experiments and of clinical studies with human beings, presumptive evidence for the indispensability of pantothenic acid in the human diet already exists.

Historical Background:

The discovery of pantothenic acid had its beginnings in early studies on the nutritional requirements of growing yeast cells. Studies on yeast have contributed greatly to information gained in nutrition and indeed in the broader field of biology. As Williams (1) has said:

> "Some of the most far-reaching discoveries in the whole field of biology have been made in connection with the study of yeasts. The fruitful doctrine of the microbial origin of human and animal disease had as its forerunner the studies of Pasteur on the 'disease of wine' which could be 'cured' by avoiding microbial contamination of the yeast cultures. Likewise the familiar doctrine that disease may be caused by lack of vitamins had its forerunner ten years before Funk's promulgation of the 'vitamin hypothesis' in the studies in Ide's laboratory in Louvain, where it was discovered that yeast required for its proper nutrition traces of a mysterious substance (or substances) which was called 'bios.' "

The discovery of the hypothetical yeast-growth factor "bios" in 1901 by Ide (2) and his student, Wildiers (3) in Belgium, represents one of the earliest recorded manifestations of vitamin activity, although it was not recognized as such at the time. For a few years following this discovery, speculation as to the actual existence, nature and significance of the hypothetical "bios" appeared in scientific literature. Other chemists, however, failed to pursue experimentally the investigation of the bios problem, so that the discussions and controversies concerning this mysterious substance soon petered out and bios was temporarily forgotten in chemical literature.

Soon after the formulation about 1911 of the concept of the vitamins, factors indispensable to animal life, came the suggestion that bios, said to be indispensable for the growth of yeast, might be a substance or group of substances similar to or even identical with the vitamins (4).

This assumption renewed interest in the study of bios and gave great impetus to further investigation of the problem. Solution of the mystery of bios, complicated by many confusing factors, proceeded very slowly. Unrecognized differences in the responses of various "strains" of what was regarded as one species of yeast, differences in experimental methods and the unsuspected presence of extremely potent traces of "bios" factors in biological materials thought to be "pure" single substances, were among the factors hindering rapid progress.

Slow as it has been, progress in the identification of bios and the constituents contributing to its activity has been remarkably fruitful. Now, more than forty years after discovery of the "bios effect" chemical investigation has revealed the presence in bios concentrates of at least five active yeast growth factors, all of which are now known to be important vitamins for animals and human beings. These are thiamin, biotin,* inositol, pyridoxine and pantothenic acid. The particular "bios effect" described by the Belgian scientists has, in fact, been attributed chiefly, if not entirely, to the pantothenic acid component of bios, and it is for this reason that pantothenic acid assumes a unique place in the early history of the vitamins. The present Review is concerned with the nutritional significance of pantothenic acid the discovery of which was a direct outgrowth of the early work on bios.

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* The discovery of biotin from the original "bios" is described in *Borden's Review of Nutrition Research*, February, 1943.

Discovery of Pantothenic Acid:

About fifteen years ago, R. J. Williams and a group of coworkers at the University of Oregon were engaged in a study of the nutrilite* requirements for various strains of yeasts. Among the yeasts studied, was the strain originally used by Wildiers in Belgium and said to require "bios" for its growth. These investigators set about determining the nature of bios, the first step being a fractionation of the concentrate by electrolytic means (6) into two separate substances, one acidic and the other basic in nature. The acid fraction of bios, which contained the active factor, was then tested for its growth-stimulating effect on a seeding of a specially selected yeast strain ("Gebrüde Mayer" strain of *Saccharomyces Cerevisiae*) (7). The addition of the bios "acid factor" in the form of a rice bran extract resulted in a tremendous stimulation of the growth of the yeast cells

Fig. 1 Effect of the Acid Substance on Yeast Multiplication (Yeast Seeding, 0.00004 mg./1cc)

Amt. (mg.) of rice bran extract added to 1cc. of synthetic medium	Yeast crops; mg. per cc. after 18 hrs.	Fold increase
0.00	0.00045	11
.00	.00052	12
.02	.00250	60
.04	.007	175
.08	.017	425
.16	.023	560
.32	.058	1,450
.64	.104	2,600
1.28	.111	2,775
2.56	.143	3,560
5.0	.285	7,125
10.0	.46	11,500
20.0	.49	12,250
40.0	.64	16,000

—from Williams *et al* (7)

* Because the term "vitamin" has been used almost universally to designate organic substances which in minute amounts are important in *animal* nutrition, the term "nutrilite" was coined by Williams (5) to include organic substances which, in minute amounts, function in a similar manner for other types of organisms.

Encouraged by this success, they conducted similar tests with ex tracts prepared from biological materials other than rice bran. The results of all of their experiments with extracts of very diverse bio logical origin (from rice bran, beef liver, crab and sea urchin eggs oysters, earthworms, molds, bacteria, egg white, milk) pointed very strongly to the existence of the same, single acid substance in all of these materials (and, they concluded, presumably in all biological tissues) which is capable of stimulating yeast growth in a very striking way. Although derived from such widely different sources, all of the extracts behaved similarly and exhibited closely identical chemical and biological properties, thus confirming the assumption that one active acid substance was common to all. Because of the apparent widespread, if not indeed universal, occurrence of this acid in bio logical materials, it was named "pantothenic" acid, from the Greek meaning "from everywhere."

Early Chemical Identification: The announcement of pantothenic acid as a distinct substance in bios concentrates, possessing marked growth-stimulating properties for yeast, marked the beginning of an exciting and difficult search for this factor in pure form. A great many clues as to its chemical identity were already available from prelimi nary studies: it was known to have distinct acid properties, a mole cular weight estimated to be between 150 and 200, and a molecular structure containing no olefin double bond, and no aldehyde, ketone, sulfhydryl, basic nitrogen, aromatic or sugar group (7). It was said to contain more than one hydroxyl group (7) and probably a nitro gen atom (not at first suspected) with barely detectable basic prop erties (8).

Isolation: While the investigation revealing the properties of pan tothenic acid were underway, attempts were being made in Williams' laboratory to further concentrate the active extracts in order to facili tate isolation of the material in pure crystalline form. This proved to be an almost impossible task. In the first place, no techniques were available for isolating this type of acid. Further, the material was exceedingly water-soluble, highly unstable in the acid form and had no outstanding identifying characteristics (such as color or reducing properties). Considerable ingenuity and time were involved in over coming these difficulties, with the result that pantothenic acid was finally concentrated and "purified" in amorphous form (9). (About 3 grams of 40% pure material as the calcium salt, and subsequently small amounts of 90% pure salt, were isolated from 250 kilograms

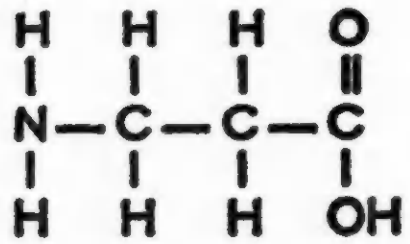
of sheep liver, or about one-tenth of an ounce of calcium pantothenate from about 550 pounds of liver.) The isolated material exhibited a potency of 11,000 as compared with a standard rice bran extract chosen as unity.

While this work was going on, investigators in three other laboratories, working on unrelated problems, reported progress in the isolation of what ultimately proved to be pantothenic acid. Koehn and Elvehjem (10), in concentrating an "anti-pellagra factor" for chicks, reported the concentration of a liver extract which was subsequently shown to have contained at least five percent of pantothenic acid. At about the same time, Snell and coworkers (11) reported on a preparation acting as a growth factor for lactic acid bacteria which was later identified as having contained about 20% pantothenic acid. A third group in England (12), working on a liver filtrate factor for rats, next reported that they had obtained a preparation which was soon found to have been 25% pantothenic acid. Thus the work of investigators in four different fields of study, involving yeasts, bacteria, chicks and rats, and supposedly concerned with four different nutritional entities, was gradually converging toward the discovery of a common biologically active substance—pantothenic acid.

Synthesis: One of the unusual features in the investigation of pantothenic acid is the fact that so much regarding its chemical nature and structure had already been determined (1933) before it was obtained in pure form. In fact, the complete structure was known and the vitamin synthesized before either pantothenic acid or its salts were obtained in sufficiently pure condition as to yield the correct analyses. (The "pure" amorphous product isolated in 1938 was actually not more than 90% pure and its analysis led to the calculation of a formula later found to be inaccurate).

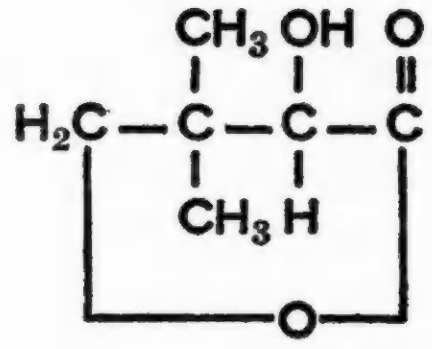
The early chemical analyses of pantothenic acid concentrates paved the way for the later determination of its exact chemical structure and synthesis. The first definite step came in 1938 with the discovery that β-alanine (Fig. 2) is a cleavage product (13). β-alanine in minute amounts had been found, two years previously, to be a yeast growth stimulant and it was now recognized as constituting a "building stone" utilized by yeast for the production of pantothenic acid. Two years later, in 1940, the other cleavage product of the pantothenic acid molecule was found to be a lactone. The lactone, a known chemical compound, (Fig. 3) was subsequently isolated in pure form (14, 15).

Figure 2



β-alanine

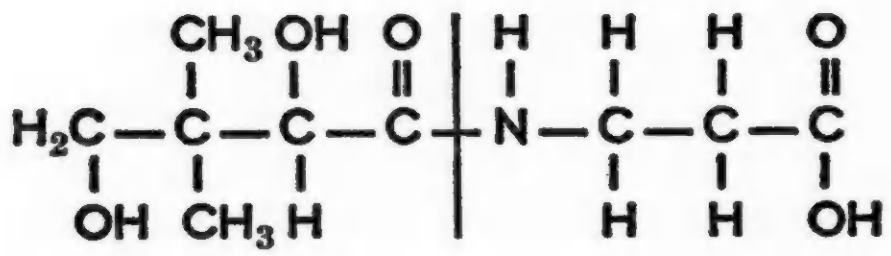
Figure 3



α-hydroxy-β, β-dimethyl-γ-butyrolactone

It was then a relatively simple matter to isolate and synthesize the β-alanine, combine it with the lactone and obtain the pure, synthetic pantothenic acid (16). All of this work was rapidly achieved during the course of one year, 1940, through the combined efforts of various investigators throughout the country, including Williams, now at the University of Texas, and a group of research chemists (16) at the Merck Research Laboratories.

Figure 4



Pantothenic Acid

Physiological Significance of Pantothenic Acid:

Long before its significance as a vitamin substance for animals and human beings was recognized, the influence of pantothenic acid in the physiological processes of various living organisms was noted. The earliest recognition of such influence occurred in 1901 with the original discovery of the hypothetical yeast growth factor "bios" (3). It was not until thirty years later, however, that the single substance, pantothenic acid, was identified as the chief factor responsible for the particular "bios effect" described by Wildiers (6, 7). Later in 1937, Snell, Strong and Peterson (11) described an "accessory factor" necessary for the growth of lactic acid bacteria, which was subse-

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quently shown to have been a pantothenic acid concentrate. This was the first indication of the importance of pantothenic acid for living matter other than yeasts. (The importance of pantothenic acid in the nutrition of other bacteria and yeasts, as well as molds, green plants and additional miscellaneous organisms has been reviewed by Williams (17, 18).

The earliest indications of the importance of pantothenic acid in animal nutrition were obtained about 1929 with the discovery of "vitamin B_3" (19), an unidentified factor essential for pigeons, whose effect is now known to have been due, in large part, to pantothenic acid. During the following three years, a characteristic dermatitis in chicks was discovered (20, 21) and found to be, in subsequent years, a manifestation of pantothenic acid deficiency. By 1939, the identity of the "chick antidermatitis factor" with pantothenic acid was simultaneously indicated by Woolley *et al* (22) on the basis of chemical studies, and by Jukes (23) on the basis of chick tests in which pantothenic acid concentrates were successfully used in place of the unidentified "chick antidermatitis factor." In the same year pantothenic acid was also shown to be essential for the proper growth of rats (12, 24) and the first indications as to its possible role in the graying of hair in rats had already been obtained (25).

Deficiency Symptoms of Pantothenic Acid: Among the numerous symptoms which have been fairly well established as connected with pantothenic acid deficiency in fowls and other animals, Williams (17) cites the following:

> Dermatitis; keratitis; adrenal hemorrhage, atrophy and necrosis; cortical fat depletion; "blood caked" whiskers; depigmentation of hair or feathers; failure to grow; loss of weight in adults; loss of appetite, emaciation; loss of coordination; loss of hair (alopecia); thymus involution; fatty livers; stomach and intestinal ulcers, diarrhea; heart damage; kidney damage; anemia; rapid respiratory rate; rapid heart rate; prostration or coma; sudden death; convulsions; gastro-intestinal symptoms; loss of viability (eggs); paralysis; myelin degeneration, sciatic nerve and spinal cord damage; peripheral neuritis; sores about the nose and mouth; hemorrhages under the skin, severe oral lesions; abnormal cartilage (tibia); spinal curvature; increased appetite for salt.

On the basis of these manifestations, Williams concludes: "It seems reasonable that only the lack of a substance fundamental to cellular physiology in general, could cause such diverse symptoms." This conclusion is given added weight by the finding that every single tissue in pantothenic acid-deficient chicks (and, according to the in-

vestigators, presumably in other deficient animals as well), exhibit evidence of the deficiency. It is further suggested that in different species, particular tissues vary quantitatively in degree of susceptibility or resistance to pantothenic acid deficiency, thereby accounting for the different deficiency symptoms exhibited by various animals.

Fundamental Biological Role of Pantothenic Acid: The manner in which pantothenic acid functions in the living organism is still a matter of considerable speculation. Some evidence exists to indicate that it may be involved in the mechanism of carbohydrate metabolism, presumably as part of a complex enzyme system (17). Observations on the effect of pantothenic acid on various metabolic processes in bacteria, yeast and green plant systems, combined with the known enzyme relationships of other B vitamins (thiamin, nicotinamide and riboflavin) lend support to this supposition.

Studies, by Supplee (26) on rats, and by Spies *et al* (27) on human beings, indicate further that an intimate physiological relationship exists between the activity of pantothenic acid and that of riboflavin. In the case of rats it was found that during the assimilation of food there is a marked mobilization of riboflavin in the liver, and that this process is directly and specifically influenced by pantothenic acid. In man it has been found, that administration of large doses of pantothenic acid is accompanied, not only by a rise in the pantothenic acid content of the blood, but by an unexpected increase, ranging from 20 to 30 percent, in the blood level of riboflavin as well. Likewise, the administration of riboflavin has been found to be accompanied by an increase in blood levels of pantothenic acid.

All of these facts, are merely suggestive of the *nature* of the role played by pantothenic acid in human and animal physiology. They are nevertheless, completely indicative of the fact that pantothenic acid—originally recognized as a nutrilite for growing yeasts—probably plays an important role in the vital economy of all living organisms.

The role of pantothenic acid in the nutrition of animals and of man will be discussed in the March, 1944 issue of *Borden's Review of Nutrition Research*.

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NEWS DIGEST

PYRIDOXINE AND NAUSEA IN PREGNANCY – Injections of pyridoxine hydrochloride (vitamin B_6) either intramuscularly or intravenously, have been used successfully in treating the nausea and vomiting which frequently complicate pregnancy. Reports of clinical trials with the vitamin indicate that complete or at least partial relief was obtained in many cases which failed to respond to other clinical means including sedatives, bed rest, restricted fluid intake, administration of vitamin B_1, and injections of glucose. In one series of 37 patients, only four failed to show any response to pyridoxine therapy. In another series of clinical studies, the following responses were obtained:

Condition	*Patients treated*	*Completely relieved*	*Partially relieved*
morning nausea	16	14	2
nausea all day	6	6	—
nausea; occasional vomiting	4	3	1
severe nausea and vomiting preventing retention of fluids	6	6	—

In all cases, an initial dose of 50 or 100 mg. of pyridoxine hydrochloride was administered intramuscularly, followed by injections of 50 or 100 mg. three times weekly until nausea subsided. The largest total amount given to any one patient was 1050 mg. The procedure should render hospitalization even of severe cases unnecessary, thereby permitting inexpensive treatment at home. Sedatives and adequate dietary supervision are still recommended as an integral part of a therapeutic regimen in which pyridoxine is regarded as a valuable, basic factor. Clinical Excerpts *17*, 234 (1943).

VITAMIN C IN MASHED POTATOES–British research workers have reported recently that the preparation of mashed potatoes may be accomplished without significant loss of vitamin C, if properly done. Inasmuch as vitamin C is easily oxidized, cooked potatoes should be mashed quickly and served immediately to avoid unnecessary contact with air. In this way, only very small quantities of the vitamin C are lost. Mashing large quantities of potatoes increases the time of operation and may, therefore, result in greater vitamin C losses. Additional tests showed that keeping mashed potatoes hot between the times of preparation and serving (as in cafeterias or when "holding dinner") greatly accelerates loss of the vitamin C. Mashed potatoes held at room temperature, on the other hand, lose only a small fraction of the vitamin C content. For this reason it is suggested that mashed potatoes which must be held for some time, be allowed to cool and then reheated just before serving. *Nature 151*, 473 (1943).

SPROUTED CEREALS AND B VITAMINS – Recent studies comparing the vitamin B complex content of cereal grains before and after germination reveal marked increases in the amounts of these vitamins in the sprouted grain. Among the cereals tested were oats, wheat, barley and corn. All showed substantial increases in riboflavin and niacin content, with somewhat lesser increases in the case of biotin, pantothenic acid, folic acid and inositol. The thiamin content remained almost constant in most instances.

	Milligrams per 100 grams dried seeds		
	Thiamin	*Riboflavin*	*Niacin*
Oats	1.13	0.08	0.75
Sprouted Oats	1.22	1.16	4.40
Wheat	0.70	0.13	6.20
Sprouted Wheat	0.90	0.54	10.30
Barley	0.68	0.09	6.75
Sprouted Barley	0.90	0.72	11.50
Corn	0.55	0.11	0.95
Sprouted Corn	0.51	0.43	3.95

It is possible, as a result of the information revealed in these experiments, that changes in present methods of utilizing cereal grains may be established in order to secure maximum vitamin values from these foods for animal and human nutrition. *Sci. 97,* 562 (1943).

THIAMIN IN FROZEN PEAS AND CORN—Frozen peas and corn, it is reported, can be stored for as long as one year without any loss in thiamin content. The storage temperatures used in these studies ranged from 0 to -10° F. Fresh peas and fresh, unhusked corn, it was found, can be held for at least five hours at ordinary room temperature without loss of thiamin. Cooking fresh or frozen peas and corn does not result in loss of thiamin when the amounts of the vitamin retained in the cooked vegetables and cooking water are taken into consideration. Increasing the amounts of cooking water causes an increase in the amount of thiamin dissolved in the water. Fresh or frozen peas and corn, if stored and cooked properly, contribute fair amounts of thiamin to the diet. *Food Research 8,* 420 (1943).

ASCORBIC ACID, DETOXICANT—A report from India suggests that ascorbic acid may have, in addition to its vitamin functions, a role as a detoxicant similar to glucuronic acid. Conjugation of toxins with glucuronic acid is a normal physiological mechanism whereby certain poisons are excreted in the urine as harmless glucuronates. Experimental evidence indicates tha following injection of animals with sub lethal doses of diphtheria or tetanu toxin an abnormally large amount o ascorbic acid is excreted in the urine i combined form. Further, patients suffe ing from acute pulmonary tuberculosi have a heightened elimination o combined ascorbic acid. These fact combined with the observation tha considerable amounts of combined as corbic acid are excreted normally also led to the investigation of how far ascor bic acid may play a role in detoxicatio mechanisms. It was found that poison ing by histamine, phenol and campho was accompanied by an increase in ex cretion of combined ascorbic acid and amelioration of the symptoms of poison ing. The process was found to be appar ently selective, inorganic poisons, in general, not being detoxified. The tenta tive conclusion has been reached that the conjugation of ascorbic acid with the toxic products of metabolism may be a normal biochemical process and tha this process for the removal of toxic substances may have added significance when infection from outside takes place. *Ann. Biochem. and Exp. Med. 1,* 6 (1941).

GUAVAS RICH IN C—The guava, a tropical fruit, has been found to be ex traordinarily rich in vitamin C. It is estimated that about four ounces of dried guava would provide sufficient vitamin C to protect an Arctic explorer from scurvy for about three months. The vitamin C content of guavas can best be preserved by blanching the unpeeled, quartered fruit after removal of the central pulp and stones. Guava powder is now being used by British troops as a rich source of the vitamin and it seems likely that the fruit may become popular in the United States as well. *Abstr. in J. Amer. Diet. Assoc. 20,* 50 (1943).